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EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 03/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,054	LALANNE ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,21,24,25 and 27-29* is/are pending in the application.

4a) Of the above claim(s) *11,18,21,24,25 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-17,27 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment and response filed 1-5-04 has been entered into the record. Claims 1-18, 21, 24, 25 and 27-29 are pending. Claims 19, 20, 22, 23 and 26 have been cancelled.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in France 99/07250 on 6-9-99.

Specification

The disclosure is objected to because of the following informalities: the disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Information Disclosure Statement

The information disclosure filed 2-15-02 has been considered. A initialed copy is enclosed.

Election/Restrictions

Applicant's election with traverse of Group 5, claims 1-10, 12-16, 27 and 29 (in part) is acknowledged. The traversal is on the ground(s) that the European examiner found unity of invention corresponding to groups 5, 11 and 18 designated by the U.S. Examiner. This is not found persuasive because these groups fail to share the same technical feature as recited in the Lack of Unity requirement and that any presumed technical feature must be "special", by defining over the art. The claims as amended still do not define over the art (see art rejections set forth below) and moreover, the groups of inventions (5, 11 and

18) fail to share the defined technical feature in common. The examiner is not misinterpreting the Rule and is not bound by Actions by the International examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 11, 18, 21, 24, 25 and 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement.

Claim Objections

Claims 27 and 29 are objected to because of the following informalities: the claims include non-elected subject matter (i.e. proteins or antibodies). Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 2, 3, 4, 5, 6, 7, 8, 9, 10 and 27 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Each of the rejected claims are drafted in independent form using the indefinite article "A" and as such are not viewed as reading the limitation of "isolated" from claim 1 into these claims. As such, these claims are necessarily drawn to a products of nature, since polynucleotides are produces of nature. Products of nature are not patentable because they do not reflect the "hand of man" in the production of the product or manufacturing process. Diamond v. Chakrabarty, 206 USPQ 193 (1980). Additionally, purity of naturally occurring product does not necessarily impart patentability. Ex parte

Siddiqui 156 USPQ 426 (1966). However when purity results in new utility, patentability is considered. Merck Co. V. Chase Chemical Co. 273 F. Supp 68 (1967). See also American Wood v. Fiber Disintergrating Co., 90 US 566 (1974);American Fruit Growers v. Brogdex Co. 283 US 1 (1931); Funk Brothers Seed Co. V. Kalo Innoculant Co. 33 US 127 (1948). Filing of arguments and evidence of a new utility imparted by the increased purity of the claimed invention *and amendment to the claims to recite the essential purity* of the claimed products is suggested to obviate this rejection. For example for claim 2, "An isolated DNA..." would be acceptable or means of providing for proper antecedent basis to claim 1 would also be acceptable "The isolated polynucleotide of claim 1, wherein the isolated polynucleotide is DNA". Additionally, the language "use of" is not statutory since it fails to set forth a statutory category of invention. As previously set forth, use of language has been interpreted as a product claim for prior art purposes.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 12-16, 27 and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification broadly describes as part of the invention isolated polynucleotides comprising a nucleotide sequence encoding the a polypeptide having the same function and having an amino acid sequence homologus with the sequence SEQ ID NO:12 or PCaNL260 (see specification page 10, lines 16-32). The function of the protein whose sequence is as set forth in SEQ ID NO:12 is not taught, nor described by the specification. The specification also broadly describes a the nucleic acid of protein gene specifically, by reference to the polynucleotide sequence set forth in SEQ ID NO:11. The specification broadly describes polynucleotides encoding the polypeptide of SEQ ID NO:2, to specifically include continuous or discontinuous regions encoding the polypeptide and may also contain additional coding and non coding regions reciting "gene" (see page 10, last paragraph and instant claims 5 and 29). It is evident from these pages, that the specification is describing the Candida albicans protein gene specifically, by a reference to polynucleotide sequence SEQ ID NO:11 and generically by reference to a polynucleotide sequence that encodes the polypeptide sequence of SEQ ID NO:12 and that such language is intended to encompass the "gene" and those coding or non-coding sequences (see claims 5 and 29 for example). The specification also broadly describes the invention as embracing any substitution, insertion or deletion change of nucleotides throughout the entire stretch of nucleotides found in the a polynucleotide of SEQ ID NO:11 or a protein homologous to SEQ ID NO:12. The claims encompass polynucleotide sequences *comprising* SEQ ID NO:11, *comprising* sequences encoding SEQ ID NO:12, sequences that have a recited degree of change as compared to an undefined nucleic acid sequence (i.e. claim 1,"... 50% identity with a polynucleotide coding for a polypeptide having the same function and having an amino acid sequence homologous with the sequence SEQ ID NO:12..."). These isolated polynucleotide variants correspond to sequences from the operon/gene, other

species, mutated sequences and allelic variants. None of these sequences meets the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

The specification only discloses a polynucleotide sequence consisting of SEQ ID NO: 11 which corresponds to the polynucleic acid sequence encoding the putative full open reading frame of *Candida albicans* species of the protein PCaNL260 that consists of the amino acid sequence set forth in SEQ ID NO:12. An isolated polynucleotide consisting of a nucleotide sequence encoding SEQ ID NO:12, is also described by way of the written description in view of the art established principle of wobble variants of triplet codons for particular bacterial amino acids as described in basic textbooks. Thus, only an isolated polynucleotide sequence consisting of SEQ ID NO: 11 and an isolated polynucleotide consisting of a nucleotide sequence encoding SEQ ID NO:12 meets the written description provision of 35 U.S.C. 112, first paragraph for the reasons set forth below.

The specification has not described nor disclosed the "gene" which encodes the protein of SEQ ID NO:12 or PCaNL260 as is claimed. As to the gene elements, a functional gene encompasses much more than a protein coding region. A gene is conventionally associated with positive and negative controlling elements such as promoters and repressors in a regulated transcription unit, without which, no protein is expressed. A gene is also broadly defined in the art as a segment of DNA involved in the production of a polypeptide chain which includes regions preceding and following the coding regions (i.e. leader and trailer) as well as regions in between individual coding segments (i.e. introns; see Lewin, B., GENES IV, Oxford University Press, 1990, page 810). The

specification fails to describe the functional gene *per se* and which applicants have intended to be encompassed by the language of the instant claims and description of the specification as set forth *supra*. In a genome, the recitation of "comprising" a structural gene of SEQ ID NO:11 or comprising a nucleic acid encoding SEQ ID NO:12, include regulatory sequences which are essential to the operation and function of the structural gene. These regulatory and other gene sequences of the operon that are not described, are essential to the function of the structural gene encoding the claimed proteins and are therefore essential elements. Such "gene" sequences fail to have an adequate written description in the instant specification. The specification does not provide written description support for any controlling flanking nucleic acid sequences which are 5' or 3' of SEQ ID NO:11 or that gene which encodes SEQ ID NO:12. The specification does not provide any polynucleotide structure for the gene segment of the *Candida albicans* PCaNL260 protein or the gene in the chromosome as conventionally accompanied by the regulatory elements (i.e., regulatory regions such as promoters or repressors, termination codon), and which comprises SEQ ID NO:11. The specification fails to teach a single variant of a polypeptide sequence of SEQ ID NO:12 and it is noted that the claimed polynucleotides do not exist as an invention independent of their function in encoding the polypeptide of SEQ ID NO:12. The actual structure or other relevant identifying characteristics of each nucleic acid that encodes a variant protein having the claimed properties of a protein can only be determined empirically by actually making every nucleic acid that encodes the recited variability (i.e. the substitutions, insertions or deletions as compared to SEQ ID NO:11) and testing each to determine whether it encodes a protein having the disclosed properties. As noted in the Guidelines at Section I.A.(2):

> There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between structure and

function in the art, one skilled in the art will be able to reasonable predict the complete structure of the claimed invention from its function.

The specification proposes the converse, yet still does not meet the requirements for an adequate written description of the claimed invention. The specification proposes that the skilled artisan is to modify a known nucleic acid sequence encoding a known protein sequence and that modification would still describe applicants invention. The protein disclosed as SEQ ID NO:2 lacks any disclosed biological function. The alleged "essential" nature of the protein is not a description of its biological function. The protein has specific biological properties dictated by the structure of the protein and the corresponding structure of the structural nucleotide sequence which encodes it. There must be some nexus between the structure of a nucleotide sequence, the structure of the protein encoded, and the function of that encoded protein. However, function can not be predicted from the modification of the structure of the gene sequence or in this case the nucleotide sequence encoding the protein. The specification has not shown that, by modifying a reference sequence encoding a reference polypeptide as claimed, will automatically predict the production of functional equivalent and moreover, provides no description of what that biological function of the protein actually is. While it is true that, due to the nature of codon degeneracy, applicant may take a reference sequence and modify that sequence to be a different nucleic acid sequence, yet still have that nucleic acid encode protein. The specification fails to teach the structure or relevant identifying characteristics of a representative number of species of a representative number of polynucleotides encoding a representative number functionally equivalent proteins, sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed. Moreover, the specification has not disclosed any information for the gene/operon/chromosome which is 3' and 5' to the polynucleotide sequence of SEQ ID NO:11 and therefore clearly lacks written description for the broad class of

polynucleotides comprising SEQ ID NO:11 or comprising SEQ ID NO:12. Thus, the written description of the instant specification does not provide for "comprising" language. In the instant case, the specification provides only written description for a polynucleotide consisting of SEQ ID NO:11 and a polynucleotide consisting of a nucleotide sequence encoding SEQ ID NO:12. With the exception of an isolated polynucleotide consisting of SEQ ID NO:11 and an isolated polynucleotide consisting of a nucleotide sequence encoding SEQ ID NO:12, the skilled artisan cannot envision all the contemplated nucleotide sequences by the detailed chemical structure of the claimed polynucleotides because the genus is so highly variant and therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. The specification fails to provide a representative number of protein or nucleic acid variants to indicate that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the single disclosed full length species of SEQ ID NO:11 that encodes the full length SEQ ID NO:12. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Therefore, only an isolated polynucleotide consisting of SEQ ID NO: 11 and an isolated polynucleotide consisting of a nucleotide sequence encoding SEQ ID NO:12, and associated vectors, host cell and methods of production, meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. (See page 1115.)

Claims 1-10, 12-16 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polynucleotide consisting of consisting of SEQ ID NO:11, vectors comprising an insert consisting of the isolated polynucleotide, host cells comprising the vectors, the specification does not reasonably provide enablement for nucleotides comprising SEQ ID NO:11 or isolated polynucleotides having variability as compared to a first polynucleotide of SEQ ID NO:11 or functional variants of the protein of SEQ ID NO:12 or encoding the polypeptide of SEQ ID NO:12, diagnosis of fungal infection or treating disease caused by *Candida albicans*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to and encompass polynucleotides which comprise a nucleotide sequence which has a recited percent identity as compared to a nucleotide sequence of encoding a polypeptide that has the same function and a homologous sequence with SEQ ID NO:12 and associated vectors, host cells comprising the vectors and methods of production of the polypeptide and kits. These claims are not enabled for the following reasons. The written description for a full length protein is limited to only SEQ ID NO:12 which is the corresponding amino acid sequence encoded by the polynucleotide consisting of SEQ ID NO:11. The claimed proteins and fragments have no demonstrated function and the specification fails to provide any written description of the biological function of the protein, nor does it provide an assay to detect such a function. The specification fails to indicate that SEQ ID NO:2 has any biological activity of any art recognized protein and further lacks any description of any variants of a SEQ ID NO:11 or SEQ ID NO:12 which act as a functional equivalents. The specification provides no evidence that SEQ ID NO:2 has the appropriate immunogenic activity in infected animals and provides description of how to assay for such activity. The specification is also not enabled for the claimed

polynucleotide comprising SEQ ID NO:11 or variants of a polynucleotide encoding SEQ ID NO:12 or 11, because 1) the specification fails to teach where and how much variation of SEQ ID NO:11 is permitted such that the polynucleotide sequence or protein sequence encoded thereby is still able to function as to detect fungal infection and in particular the pathogen *Candida albicans* as a diagnostic or therapeutic as asserted specification; 2) the specification lacks any written description of any functionally equivalent fragments or variants of SEQ ID NO:11 or SEQ ID NO:12 as claimed which are capable of functioning as a diagnostic as asserted in the specification and lacks any discussion of the function of the polypeptide of SEQ ID NO:1 and lacks description of specific assay conditions, such as substrate, pH, temperature etc., which could be used to determine functional equivalents or fragments which are encompassed by the language of the claims; 3) the specification fails to teach how to use nucleic acid sequences which are variants of SEQ ID NO:11 in diagnosis or detection because the specification fails to teach what are the critical nucleic acid residues that can be modified and still achieve a nucleic acid that will function as a diagnostic or detection reagent for *Candida albicans* or any genus of fungal infections; 5) the art teaches that polynucleotides isolated based on percent homology do not predictably display the functions of their homologs; 6) the art teaches that even replacement of a single amino acid residue may lead to both structural and functional changes in biological activity and immunological recognition of a protein, one skilled in the art would have reason to doubt the validity functionality of the protein of SEQ ID NO:12 and any variants or fragments thereof, and the detection or diagnostic use of variants thereof, and the detection or diagnostic use of variants of isolated nucleic acids encoding variants of the isolated nucleic acid of SEQ ID NO:11 or protein of SEQ ID NO:12, and 7) the specification has not displayed a nexus between the structure of the nucleotide sequence and function of the protein or a functionally equivalent protein variant with detection or diagnostic use.

As to points 1)- 7), the specification fails to provide a written description of any nucleic acids encoding protein variants (i.e. the mature form, prepro form, the pro form) of the protein sequence of SEQ ID NO:12, which function equivalently to a polypeptide comprising the disclosed SEQ ID NO:12 or are able to be used as a diagnostic or detection reagent. The specification fails to teach the critical protein residues involved in the function of the protein SEQ ID NO:12 or that SEQ ID NO:12 has the ability to function the same as SEQ ID NO:12, because the function of SEQ ID NO:12 is not disclosed in this specification, such that the skilled artisan is provided no guidance to test, screen or make nucleic acid sequence variants of the polynucleic acids encoding the variants of the polypeptide of comprising SEQ ID NO:12 or the polynucleotide comprising SEQ ID NO:11, using conventional technology which allow for a screening or generic diagnostic use asserted in the specification. The specification fails to teach to what extent you could alter SEQ ID NO:11 and still present the sequence as diagnostic. In order to be diagnostic the sequence must distinguish *Candida albicans* from non-pathogenic eukaryotic cells. and other clinically relevant autochthonous bacteria in a host. The specification also fails to demonstrate the actual biological function of the DNA and protein and only speculates on an undisclosed function in viability based on fractional homology to other sequences. Further, viability is not a function of a protein but the phenotypic outcome of expression of the protein. For example, water is required for viability but does not describe the function of water per se. Similarly, assertion that the protein is required for viability does not describe the function of the protein per se as it relates to the biological system from which it is derived. One skilled in the art would have reason to doubt the alleged function of the protein and polynucleic acid encoding the protein because the specification fails to teach that the protein produced by the DNA actually functions as asserted and the art teaches that polynucleotides isolated based on percent homology do not predictably display the functions of their homologs. Absent factual evidence, a percentage sequence similarity of less than 100 % is not deemed to reasonably support to

one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of such a similar known biomolecule. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding enablement. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over biomolecules of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Gerhold et al.[BioEssays, Volume 18, Number 12, pages 973-981(1996)]; Wells et al.[Journal of Leukocyte Biology, Volume 61, Number 5, pages 545-550 (1997)]; and Russell et al.[Journal of Molecular Biology, Volume 244, pages 332-350 (1994)]. Even if one were to demonstrate that SEQ ID NO:12 functioned in some manner or was useful in diagnosis, the specification is not enabled for polynucleotides encoding protein variants because the specification fails to teach the appropriate substrate and assay which one skilled in the art could use to screen for polynucleic acids encoding homologous functionally equivalent variants or fragments of SEQ ID NO:12 which are encompassed by the claims. No substrate assay for function or guidance for setting forth parameters of a functional assay is set forth in the specification which would allow one skilled in the art to screen for biologically functionally equivalent variants of either the protein or diagnostic use of encoding polynucleotides or variants of SEQ ID NO:11 for specific detection and the specification does not specifically point to a particular one in the art would could be relied upon for screening for polypeptides and polynucleotides encoding them for diagnostic or screening use. One of

skill in the art would be reduced to merely randomly altering nucleic acids which would lead to unpredictable results regarding the functional activity of the nucleic acid and the ability of the nucleic acid to be used as a diagnostic reagent, detection reagent or encode a functional protein and one skilled in the art would be unable to test for functionality of the polynucleotide variants of the polynucleotide of SEQ ID NO:11. Thus, one skilled in the art could not even screen for working embodiments within the scope of the claim because no assay is apparently set forth in the specification. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted *a priori* and must be determined empirically on a case by case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3):1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of a single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which products proteins that differ in native conformation, immunological recognition, binding and toxicity, thus

exemplifying the importance of structural components to both biological function and immunological recognition. The specification has not taught which residues of SEQ ID NO:12 can be varied and still achieve a protein that is functional or is capable of use as a diagnostic using immunological means of recognition. The specification has not conceived any other functionally equivalent protein variants or fragments or the polynucleic acid sequence encoding the protein variants, does not set forth the general tolerance to substitutions, where substitutions could be made and how to assay for these variants. Since, the specification lacks a written description of any variant comprising SEQ ID NO:11 or a protein sequence of SEQ ID NO:12 which has the ability to function, it is not enabled for this language because it fails to enable the skilled artisan to envision the detailed chemical structure of the claimed polynucleotide encoding protein variants of SEQ ID NO:12 or that SEQ ID NO:12 functions as alleged, respectively, as well as the screening method of obtaining them, as well as how to use the polynucleotides encoding the protein variants, one of skill in the art would be unable to produce these polynucleotides encoding protein variants, produce a biologically active protein or polynucleotide variants encompassed by the instant claims. The art of record teaches that polynucleotides isolated based on percent homology do not predictably display the functions of their homologs absent some independent teaching that the sequence produces a protein that functions as alleged . Thus, biological function ascribed the gene product based on solely structural or sequence identity is unreliable and unpredictable in the absence of supporting production of the protein and functional analysis. There is no evidentiary support that the instant protein has use and has a biological function that can be assayed. Moreover, as to claim 6, from the definition of Applicants' invention as set forth in the specification, it is unclear exactly what the composition of any protein will be if it is expressed by a nucleic acid which has the claimed changes. For, example, if one nucleotide is deleted or inserted at a single place within the coding sequence, all the codons down stream of that insertion or deletion will be frame shifted. If that frame

shift takes place near the 5' end of the gene, it is highly likely that the protein expressed will have little in common structurally or functionally with the protein of SEQ ID NO:12. The teachings of the specification fail to allow one skilled in the art to predict what effect a given change in the nucleic acid sequence will cause. Such changes are not enabled as applicants' invention. Applicant has not enabled the scope of the invention as claimed for those nucleic acids encoding a SEQ ID NO:12 variant that would be altered, as now claimed. The specification discloses a putative protein with undisclosed biological function and a nucleic acid encoding it. The protein has specific immunological and biological properties which are the result of its primary acid sequence as encoded by this nucleic acid sequence. Applicants' proposed insertions, deletions or substitutions to that nucleic acid sequence do not predict a protein having all the identifiable properties of the protein as disclosed. Therefore, such undisclosed and unidentified nucleic acids which result from these, insertions, deletions or substitutions encompasses by the recited "insertions, deletions or substitutions" are not enabled for their scope. The skilled artisan would be forced into undue experimentation to make and use the instantly claimed scope of invention. Although the skilled artisan might envision making a great number of changes of a reference nucleic acid sequence in accordance with applicant's disclosure, it is unclear exactly that the protein which is expresses therefrom would be the protein disclosed as applicants' invention or that these altered nucleic acids would diagnose or detect the presence of a fungal infection or protect from disease. These altered nucleic acids would encode a polypeptide which would vary from the disclosed protein in some unknown or unpredictable manner. *Amgen Inc. v. Chugai Pharmaceutical Co. Inc.* 18 USPQ2d 1016, 1026 (CAFC 1991) addressed a similar issue of enablement and undue experimentation for analogs of erythropoietin (EPO) gene broadly claimed and narrowly disclosed. In that instance, it was found:

> that over 3,600 different EPO analogs can be made by substituting at only a single amino acid position, and over a million different analogs can be made by substitution

three amino acids. The patent indicates that it embraces means for preparation of "numerous" polypeptide analogs of EPO. Thus, the number of claimed DNA sequences encoding sequences that can produce EPO-like product is potentially enormous.

Further, at page 1027, the CAFC found that:

it is not necessary that a patent applicant test all the embodiments of his invention, ... what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. For DNA sequences, this means disclosing how to make and use enough sequence to justify a grant of the claims sought. Amgen has not done that here. In addition, it is not necessary that a court review all of the *Wands* factors to find a disclosure enabling. They are not illustrative, not mandatory. What is relevant depends on the facts, and the facts here are that Amgen has not enabled preparation of DNA sequences to support its all-encompassing claims... Here, however, despite extensive statements in the specification concerning all the analogs of the EPO gene that can be made, there is little enabling disclosure of particular analogs and how to make them. Details for preparing only a few EPO analogs genes are disclosed. Amgen argue that this is sufficient to support its claims; we disagree. This "disclosure" might well justify a generic claim encompassing these and similar analogs, but it represents inadequate support for Amgen's desire to claim all EPO analogs. There may be other genetic sequence that code for EPO-Type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them...[W]e do not intend to imply that genetic sequences cannot be valid where they are of a scope appropriate to the invention disclosed by an applicant. That is not the case here, where Amgen has claimed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure of hot to make EPO and a very few analogs.

Finally, at page 1028, the CAFC concludes:

> Considering the structurally complexity of the EPO gene, the manifold possibilities for change in its structure, with an attendant uncertainty as to what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity. Under the circumstances, we find no error in the court's conclusion that generic DNA sequence claims are invalid under section 112.

See also *In re Duel* 34 USPQ2d 1210 (CAFC 1995); *Colbert v. Lofdahl* 21 USPQ2d 1068 (Bd. Pat. Ap. Inter. 1991); and *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC 1997). As to claim 12, the specification lacks any written description of how to isolate and purify the protein of SEQ ID NO:12, no purification steps are disclosed, no conditions set forth in the specification. Protein purification is a highly empirical process. In the absence of specific guidance as to the particular columns and conditions effective to purify the polypeptide, one skilled in the art would have to randomly choose from hundreds of possible conditions and protein purification columns without any reasonable chance for success. The description is devoid of any teaching of how to isolate and purify any recombinant protein.

In view of the lack of written description of any protein or protein variant of SEQ ID NO:12 that functions equivalently to the protein of the art as alleged and the corresponding nucleic acid sequence, the lack of enabling description of make and use polynucleotides encoding protein variants of SEQ ID NO:12 or the lack of enabling

description of make and use polynucleotides comprising variants of SEQ ID NO:11, the lack of an enabling written description of how to obtain and make and use the nucleic acid variants of the of the polynucleotide sequence of SEQ ID NO:11, the unpredictability associated with making and using the nucleic acids encoding the myriad variants of SEQ ID NO:11 encompassed in the scope of the claims as set forth above, the lack of teaching even a beginning point for variation of the nucleic acid for routine experimentation, the lack of an assay to screen for variants, lack of working examples commensurate in scope with the instant claims, that one skilled in the art has no means of assaying for functional equivalents because the function of the protein of SEQ ID NO:12 is not taught by the specification, the skilled artisan would be forced into undue experimentation to practice (i.e. make and use) the invention as is broadly claimed.

Claims 17 and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As to claim 17, the specification lacks complete deposit information for the deposit of plasmid I-2212. Applicant's referral to the deposit of the cell line comprising the plasmid I-2212 on page 19 of the specification is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR §1.801-1.809 have been met.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant

of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of deposit and the complete name and full street address of the depository is required.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR §1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

In addition, a deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological

material not made under the Budapest Treaty must be filed in the application and must contain:

1) The name and address of the depository;

2) The name and address of the depositor;

3) The date of deposit;

4) The identity of the deposit and the accession number given by the depository;

5) The date of the viability test;

6) The procedures used to obtain a sample if the test is not done by the depository; and

7) A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the cell line described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed. Applicant's attention is directed to In re Lundack, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR §1.801-1.809 for further information concerning deposit practice.

As to claim 29, the claim requires a method of treating a disease caused by *Candida albicans* comprising administration of the gene encoding CaNL260. The specification is devoid of teaching of the immunogenicity of the protein CaNL260. There is no description that patients with *Candida albicans* actually develop an immune response to the protein. There is no evidence of record that the gene, even if translated produces a protein that is effective in treating disease caused by *Candida albicans*. The protein is broadly described

as being essential for survival and multiplication of *Candida albicans*. The description is devoid of information regarding the accessibility of the protein to the immune system. If the protein is located on the inside of the yeast, then antibodies, if generated from gene vaccination as claimed would not be able to bind the target protein and the function of the antibody to eliminate the pathogen would not happen. Further, if the protein is "essential for survival and multiplication" (page 2, lines 30-32), then production of the protein in vivo would necessarily provide for extension of the viability of *Candida albicans* and consequently production of the protein would therefore promote maintenance of a disease caused by *Candida albicans* because the protein promotes viability (continued vitality...i.e. the yeast continues to live, multiply and cause disease). Even if one were to demonstrate that administration of the gene provides for an immune response to the polypeptide of SEQ ID NO:12, the art is replete with examples that mere immunogenicity does not correlate with the generation of a protective immune response or effective treatment of disease caused by *Candida albicans* (see for example Feng et al (Infection and Immunity, 64(1):363-365, 1996) that teaches that P55, is an immunogenic but nonprotective 55-kilodalton *Borrelia burdorferi* protein in murine lyme disease). As such, one skilled in the art would have ample reasons to doubt the ability to use the claimed composition comprising the nucleic acids as a therapeutic for treating a disease caused by *Candida albicans*. The courts have held that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. (Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001). Moreover, the specification must have been enabling at the time the invention was made and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing (*In re Wright*, 27 USPQ2d 1510). In the absence of a teaching of the claimed nucleic acids are effective in treatment of disease caused by *Candida albicans*, the specification is not be enabled for such. In view of the unpredictability of the art, the lack of teachings of the specification, it would require

undue experimentation on the part of the skilled artisan to practice the invention as claimed for treatment of a disease caused by *Candida albicans*.

Claims 1-10, 12-17, 27 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claims 1-10, 12-16, 27 and 29, neither the specification nor the claims defined nor describe the "function" of the protein/polypeptide and as such the metes and bounds of the functional equivalents can not be ascertained. The assertion in the specification at page 2, lines 30-32, that the proteins are encoded by "..essential genes which are indispensable to the survival and multiplication of the cell." is not a description of the function of polypeptide in the cell. For example, water is indispensable to the survival and multiplication of any cell, but this is not a description of the structure or function of water *per se*. As such, the assertion of "essential for" is not a description of the function of the protein/polypeptide. As a corollary, the term "functional fragment" also lacks precision and clarity because the function of the protein/polypeptide is not set forth in specification nor the claims.

Claim 1 and every claim dependent thereon is unclear because SEQ ID NO:12 is not a sequence *per se* but a representation of such. As such, the claims should properly recite that ".. a polypeptide having the same function and having an amino acid sequence homologous with the amino acid sequence set forth in SEQ ID NO:12.".

As to all claims 2-10, 12-16 and 27 as apparently dependent from claim 1, the claims are confusing because they do not use proper antecedent language to provide for proper antecedent basis for the terminology in the independent claim and lends confusion as to which polynucleotide sequence is being specifically being referenced. For example, Claim 2 recites "an isolated polynucleotide", "a polynucleotide having at least 50% identity", "a polynucleotide coding for a polypeptide" and "a complementary polynucleotide".

Amendment of this claim to recite "The isolated polynucleotide of claim 1, wherein the isolated polynucleotide is DNA." would obviate this issue. Similar problems with antecedent basis confusion are present in dependent claims 3 and 4. As to claims 5, 6 and 8, there is no recited DNA sequence in claim 1 and as such "A DNA sequence of claim 1" lacks antecedent basis therein. If applicants intend to provide for dependent claims proper use of antecedent basis should be observed. "The DNA sequence of claim X, ...". Dependent claims should begin with "The isolated polynucleotide of claim X," to make it clear that the limitations of claim X flow into the dependent claims. As to claims 7 and 10, the claim makes no sense because it recites A DNA sequence coding for the protein PCaNL260 of claim 5, however claim 5 is drawn to a DNA sequence and not a protein and as such fails to properly limit and fails to find proper antecedent basis in this claim. Further, the protein does not contain a nucleotide sequence and therefore this language renders the claim confusing. Additionally, the claim recites or references multiple DNA sequences and as such it is completely unclear what specific DNA sequence is being claimed. s to claim 7, the DNA sequence which hybridizes with these and/or have significant homologies" lacks antecedent basis in the claim 5. As to claim 8, the specification does not teach the meaning of a modification introduced by suppression of at least one nucleotide and modification by suppression of a nucleotide is not an art recognized term and is not defined nor described in the specification as filed and as such the metes and bounds of the modification can not be ascertained. As to claim 9, the claim recites or references multiple DNA sequences and as such it is completely unclear what specific DNA sequence is the basis of comparison for homology calculation and what DNA sequence is compared to what individual DNA sequence. Is this drawn to the combination of two distinct DNA sequences ? The claims recite "A DNA sequence of claim 5 and a DNA sequence which...". Are applicants intending to claim a composition of two different DNA sequences? It is unclear what is actually being claimed and how this further limits the independent claim. Similar issues exist within claim 10. Further in regard to claim 10, the claim makes no

logical sense. The term "AA" has no antecedent basis in any claim from which this depends. What amino acid sequence is compared to what sequence ?. What does "at least 40%, rather at least 60%, with the AA sequences coded by said DNA sequence mean ? The metes and bounds of neither the nucleic acid nor the polypeptide can be readily ascertained. As to claim 27, the claim recite "A DNA sequence of claim 5" since there are multiple sequences it is not clear what specific DNA sequence applicants reference. As to all the claims, while acronyms can be used in the claims, it is proper to fully spell out the chemical name or institution and then follow with the acronym in parenthesis such that the acronym is unambiguously associated with an organization, protein function or chemical. Correction in all cases is required.

The examiner has presented numerous clarity, indefinite, lack of antecedent basis issues in all of the claims under examination. These issues represent only the most glaring problems with the current claims and may not represent all the specific issues present in the current claim set. Applicants are required to review the claims and present claims that have terms with proper antecedent basis and proper English such that the metes and bounds are clearly set forth.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> **(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.**

Claims 1, 2, 3, 5, 7, 8, 9, 10 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Database GenEMBL database, Accession number Z71536, Y13139, Sen-Gupta et al, publically available August 11, 1997.

The claims are so unclear that it is impossible to determine what comparison to make to achieve the 50% identity required by the claims. Because, the proteins need only be homologous and homologous is merely defined by similar function in the claims and in view of the fact that the specification nor the claims define the specific function the following art is Applied. The 50% identical is interpreted to be that the protein of the prior art must have at least one common amino acid in view of the language of "...an amino acid sequence homologous with the SEQ ID NO:12."

Sen-Gupta et al teach a nucleic acid sequence from the open reading frame YNL260c from the yeast Saccharomyces cerevisiae. The nucleic acid is encoding SEQ ID NO:12 of the claims is 58.78% similar as compared to the nucleic acid of the prior art. Because the encoding language allows for less than a 50% identity at the nucleic acid level, the nucleic acid of the prior art meets the language of the claims. Additionally, absent convincing evidence to the contrary, the proteins share the same function. Further, since the smallest functional unit of a polypeptide is an amino acid and since the nucleic acid of the art shares an amino acid in common, the art meets the limitation of functional fragment. Further, since the claims recite "a complementary" polynucleotide of polynucleotide and not "the full complement", the art meets the claims because they share a s string of identical sequence and structure in common. The RNA is readily apparent from the nucleic acid structure described in the Database.

Claims 1, 2, 3, 5, 7, 8, 9, 10 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Lin et al, PNAS, 92(9):3784-3788, 1995, nucleic acid Database GenEMBL database, Accession number L35270, publically available June 06, 1995.

The claims are so unclear that it is impossible to determine what comparison to make to achieve the 50% identity required by the claims. Because, the proteins need only be homologous and homologous is merely defined by similar function in the claims and in view of the fact that the specification nor the claims define the specific function the following art is Applied. The 50% identical is interpreted to be that the protein of the prior art must have at least one common amino acid in view of the language of "...an amino acid sequence homologous with the SEQ ID NO:12."

Lin et al teach a nucleic acid sequence from the open reading frame YNL260c from the yeast Saccharomyces cerevisiae. The nucleic acid is encoding SEQ ID NO:12 of the claims is 58.78% similar as compared to the nucleic acid of the prior art. Because the encoding language allows for less than a 50% identity at the nucleic acid level, the nucleic acid of the prior art meets the language of the claims. Additionally, absent convincing evidence to the contrary, the proteins share the same function. Further, since the smallest functional unit of a polypeptide is an amino acid and since the nucleic acid of the art shares an amino acid in common, the art meets the limitation of functional fragment. Further, since the claims recite "a complementary" polynucleotide of polynucleotide and not "the full complement", the art meets the claims because they share a s string of identical sequence and structure in common. The RNA is readily apparent from the nucleic acid structure described in the Database.

Status of the Claims

All claims stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-F 6:30 pm - 3:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Smith Lynette can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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